

**REMARKS**

This Amendment cancels claim 17, amends claims 16, 19 and 22, and adds new claims 29 and 30. Page 8, lines 3-5 of the specification support the local inflammatory disease or disorder feature of claim 16, while page 8, lines 16-17 support the local administration feature of claim 22. The amendment of claim 19 merely changes the dependency of that claim. New claims 29 and 30 are supported by page 6, lines 10-17. Claims 16, 19-22 and 28-30 are pending.

This Amendment overcomes the 35 U.S.C. § 112, first paragraph, rejection of claims 16, 17 and 19-22 for non-enablement. More particularly, claim 16 now defines a method of treatment. Reconsideration and withdrawal of the non-enablement rejection of claims 16, 17, and 19-22 are earnestly requested.

This Amendment also overcomes the 35 U.S.C. § 112, second paragraph, rejection of claims 16, 17, 19-22 and 28 for non-enablement. "Essentially" has been deleted from claim 16, thereby overcoming the sole ground for rejection. Reconsideration and withdrawal of the indefiniteness rejection of claims 16, 17, 19-22 and 28 are earnestly requested.

The 35 U.S.C. § 112, first paragraph, rejection of claims 16, 17 and 19-22 for failure to comply with the written description requirement is traversed. Page 6, lines 7-17 of the application provide a written description that any pharmaceutically acceptable, non-toxic agent having its dissociation constant in the range 6.7 to 7.4 and able to accumulate inside a cell has utility in the claimed method. Such agents may be inorganic or organic, preferably an organic acid having a heterocyclic ring with a saturated or, more preferably, an unsaturated carboxylic acid moiety. Suitable heterocyclic groups such as thiazole, thiophene, furan, oxazole, triazole, tetrazole, pyrazole, pyridine, pyrimidine and triazine are specifically identified.

This written description demonstrates the inventors had possession of the claimed invention as of the filing date of the application. Reconsideration and withdrawal of the written description rejection of claims 16, 17 and 19-22 are respectfully requested.

The 35 U.S.C. § 102(b) rejection of claims 16, 17, 19-22 and 28 over U.S. Patent No. 5,494,676 to Stab et al. is traversed. The claimed method includes administration of a pharmaceutical composition comprising a pharmaceutically acceptable agent or salt

thereof capable of acidifying cell cytoplasm, wherein the agent is mixed with a carrier to adjust the pH of the composition to a pH range of 6.1 to 7.0.

Stab et al. fails to disclose a pharmaceutically acceptable composition comprising a pharmaceutically acceptable agent or salt thereof capable of acidifying cell cytoplasm, wherein the agent is mixed with a carrier to adjust the pH of the composition to a pH range of 6.1 to 7.0. As previously noted, Col. 7, lines 24-29 of Stab et al. mention cis-urocanic acid was made from trans-urocanic acid by isomerization in distilled water buffered with NaOH to pH 6.9. However, this is the pH of the reaction medium during cis-urocanic acid synthesis; it is not the pH of a pharmaceutical preparation containing cis-urocanic acid and other ingredients.

The Applicants have prepared two formulations (Cream A and Cream B) of Experiment 1 of Stab et al. The pH of cream A (containing uraconic acid) was 4.74, while the pH of placebo cream B was 7.79. See the attached Declaration Pursuant to 37 C.F.R. 1.132 by Dr. Jarmo Laihia.

Neither cream A or B has a pH within the range 6.1 to 7.0. Reconsideration and withdrawal of the anticipation rejection of

claims 16, 17, 19-22 and 28 over Stab et al. are earnestly requested.

The 35 U.S.C. § 103(a) rejection of claims 16, 17 and 19-22 over Ben-Bassat et al., "Inhibitors of Tyrosine Kinases in the Treatment of Psoriasis", 6 Current Pharm. Design 933-942 (2000) is traversed. The claimed method of treatment administers a pharmaceutical composition comprising a pharmaceutically acceptable agent or salt thereof capable of acidifying cell cytoplasm to a person or animal in need thereof.

Ben-Bassat et al. fails to raise a prima facie case of obviousness against the claimed method because the reference fails to disclose or suggest administration of a pharmaceutical composition comprising a pharmaceutically acceptable agent or salt thereof capable of acidifying cell cytoplasm, i.e., able to dissociate a proton once in the cell. Instead, Ben-Bassat et al. cite Dvir et al., 113 J. Cell. Biol. 857-865 (1991) [Ref. 79], who studied the effect of tyrphostin compounds (including compound AG 18) on human and guinea pig keratinocytes. In their experiments the compound was dissolved in a standard cell culture medium solution before administration to the cells. In this regard, all common cell culture media contain buffering agents to maintain the

pH at 7.4. It is known that normal intracellular pH is in the range of 7.2 to 7.4. It must be assumed that when compound AG 18 was tested by Dvir et al. both the extracellular and intracellular pH was kept at pH 7.4, as there is no mention of pH adjustment in the experimental section. Accordingly, the movement of AG 18 molecules into the cell cytoplasm would not change the molecule's protonation status, because the pH environment inside the cells is the same as the pH environment outside the cells. Furthermore, the question whether AG 18 was in dissociated or non-dissociated form is irrelevant, as there would have been no change in the molecule when it moved from extracellular environment to the cell's cytoplasm.

Dvir et al. stress the specificity of tyrphostin compounds for protein tyrosine kinases, name then as tailor-made protein kinase inhibitors or blockers, and suggest that tyrphostin compounds compete with intracellular substrates of EGF receptor kinase activity (Dvir et al., p. 857-864). This disclosure suggests that the tyrphostin compounds act as typical enzyme inhibitors, which bind to an active or regulatory site of the enzyme molecule, preventing physicochemical interaction between the enzyme and its substrate molecule.

In short, the antipysoriatic effect of the molecules cited in Ben-Bassat et al. is not based on the same mechanism (acidifying the cytoplasm) as the compounds of the present invention. One of ordinary skill in the art is given no motivation or suggestion to administer a pharmaceutically acceptable agent or salt thereof capable of acidifying cell cytoplasm to treat a local inflammatory disease or disorder from either Ben-Bassat et al. or the Dvir et al. article cited therein. Reconsideration and withdrawal of the obviousness rejection of claims 16, 17 and 19-22 over Ben-Bassat et al. are earnestly requested.

The provisional obvious-type double patenting rejection of claims 16, 17 and 19-22 over claims 13-18 and 20-23 of copending Application S.N. 11/408,056 in view of Granstein, "Psoriasis: Further Evidence of a Key Role for Leukocytes," 98 J. Clin. Invest. 1695-1696 (1996) is respectfully traversed. As noted in the Official Action, the allegedly conflicting claims have not yet been allowed. Since this application is in condition for allowance, the rejection should be withdrawn. A corresponding non-provisional rejection can then be made in the '056 application, if appropriate. Reconsideration and withdrawal of the provisional, obvious-type double patenting rejection of claims 16, 17 and 19-22 over claims

13-18 and 20-23 of the '056 application in view of Granstein are earnestly requested.

The provisional obvious-type double patenting rejection of claims 16, 17 and 19-22 over claims 16-21 and 23-26 of copending Application S.N. 10/565,202 in view of Granstein is respectfully traversed. As noted in the Official Action, the allegedly conflicting claims have not yet been allowed. Since this application is in condition for allowance, the rejection should be withdrawn. A corresponding non-provisional rejection can then be made in the '202 application, if appropriate. Reconsideration and withdrawal of the provisional, obvious-type double patenting rejection of claims 16, 17 and 19-22 over claims 16-21 and 23-26 of the '202 application in view of Granstein are earnestly requested.

It is believed this application is in condition for allowance. Reconsideration and withdrawal of all rejections of claims 16, 17, 19-22 and 28, and issuance of a Notice of Allowance directed to claims 16, 19-22 and 28-30, are earnestly requested. The Examiner is urged to telephone the undersigned should he believe any further action is required for allowance.

A Petition and fee for a one month Extension of Time are attached. It is not believed any additional fee is required for

U.S. Appln. S.N. 10/534,988  
AMENDMENT

**PATENT**

entry and consideration of this Amendment. Nevertheless, the Commissioner is authorized to charge our Deposit Account No. 50-1258 in the amount of any such required fee.

Respectfully submitted,

/James C. Lydon/

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Enclosures:

Petition for Extension of Time  
Declaration Pursuant to 37 C.F.R. 1.132  
Dvir et al., 113 J. Cell. Biol. 857-865 (1991)